REMARKS

Claims 7-32 are pending in this application, as previously shown. Claims 20-32 have been withdrawn from consideration pursuant to an election of species requirement.

UNENTERED AMENDMENTS

The Examiner continues to maintain that FIG. 12 and Applicants' amendments to introduce sequences into the specification represent new matter. *See,* Advisory Action, page 2, stating:

> In regard to Fig. 12: Examiner maintains that Fig. 12 represents new matter. Nowhere in specification applicant indicated [*sic*] possession of mutants of the particular sequences described in the Domenighini reference. The Domenighini reference itself is used in specification not to direct to particular sequences, but to direct to one particular residue of interest that this suggestion suggests to mutate. The disclosure as filed address strains of LT in general (p. 5, lines 5-7) and does not reduce the genus to particular species addressed in Domenighini.
>
> Consequently, amendment to specification suggested by applicant is not entered as it represents new matter as well.

The Examiner mischaracterizes the context in which Domenighini is cited in the specification.

Applicants note that the first citation of Domenighini is in the paragraph beginning on line 25 of page 5, not lines 5-7 as set forth in the Advisory Action. In any event, Domenighini is clearly and unambiguously cited in the specification for **everything** it teaches in regard to LT-A sequences, including **all** the sequences of Fig. 12 (see, specification page 5, lines 25-31, emphasis added):

> It will be appreciated that in derivatives of LT-A, such as fragments, or in LT-A proteins of different *E. coli* strains, the amino acid residue to be mutated is that which corresponds to Ala-72 **as defined for LT-A in Domenighini et al. [Molec. Microbiol. (1995) 15:1165-1167]**. Ala-72 is located on the second turn of the alpha-helix in LT-A and faces the NAD binding site.

Thus, the specification does not cite Domenighini to point to a single residue of LT-A, but, instead, uses the Domenighini reference define correct, full-length sequences of LT-A proteins that can act as reference sequences.

The Advisory Action also failed to address the fact that Applicants must be afforded the opportunity to amend their specification to include material incorporated by reference and deemed "essential." *See,* As set forth in M.P.E.P. § 608.01(p), In re Hawkins, 486 F.2d 569, 179 USPQ 157

(CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

In sum, it is legally and factually improper for the Examiner to refuse to enter the previous amendments to the specification and to continue to maintain, in the face of overwhelming evidence to the contrary, that these amendments or the previous submission of FIG. 12 somehow constitute "new matter."

35 U.S.C. § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 7-29 were again rejected as allegedly not described by the specification as filed (see, Advisory Action, paragraph bridging pages 2-3):

> Examiner maintains that the claims have not addressed particular species, fragments of particular size of particular SEQ ID NO:1. All that is described in [*sic*] specification as filed are fragments of LT-A in general. [citation to M.P.E.P. 2163.05 omitted].
>
> Note that all Domenighini reference was used for, in the much recited section of specification p. 5, lines 25+) is to point at location of Ala residue in particular location. Nowhere does specification as filed demonstrates [*sic*] possession of fragments of particular size of particular sequence, SEQ ID No. 1.

For the reasons of record and those presented below, Applicants traverse the rejection and supporting remarks.

Basis of the Rejection

The Examiner has improperly changed the basis of the written description rejection. Previously, as set forth in the Final Office Action, it was maintained that the recitation of fragments of 8 amino acids in length are not disclosed in the specification as filed. (Final Office Action, last paragraph on page 3). Now, in the Advisory Action, the Examiner asserts that the specification does not demonstrate possession of "fragments of a particular size of a particular sequence." Thus, the rejection has changed from whether the specification discloses fragments in general to whether the specification discloses particular sizes and sequences.

Fragments of Particular Sizes

However the written description rejection is phrased, Applicants are at a loss to understand how the Examiner can continue to insist that nucleotide sequences encoding polypeptide fragments of particular sizes (*e.g.*, 8 amino acids are more) are not described in the specification as filed. The Examiner's attention is again directed to page 17, lines 10-19, where it is stated:

> A polypeptide or amino acid sequence "derived from" a designated nucleic acid sequence refers to a polypeptide having an amino acid sequence identical to that of a polypeptide encoded in the sequence, or a portion thereof, wherein the portions consists of at least 3-5 amino acids, and more preferably at least 8-10 amino acids, and even more preferably, at least 11-15 amino acids, or which is immunologically identifiable with a polypeptide encoded in the sequence. This terminology also includes a polypeptide expressed from a designated nucleic acid sequence.

Thus, the specification clearly describe polypeptide fragments of 8-10 (or more) amino acids as well as polynucleotide sequences encoding such fragments. Accordingly, there is no question that the specification demonstrates that Applicants were in possession of the claimed fragment sizes at the time of filing.

Fragments of Particular Sequences

With regard to particular sequences, Applicants again note that a reference sequence is clearly recited in all claims. Thus, the particular sequence of each fragment is described.

Furthermore, the contention that reference sequences are somehow new matter (on the grounds that Applicants' citation to Domenighini can somehow be viewed as pointing to a single residue in isolation of multiple full-length sequences disclosed in this reference) is preposterous. As detailed previously and above, Domenighini is cited to define particular, correct, full-length sequences, which sequences provide a basis for alignments with other sequences to determine the corresponding Ala-72 residue. *See, e.g.*, paragraph on page 5 reproduced above. Indeed, the "much-cited" section becomes meaningless when interpreted in the manner suggested by the Examiner -- there are no possible reference sequences if Domenighini was cited for teaching a single residue in isolation.

Clearly, the only sensical interpretation of the "much-recited" section is in the manner clearly intended by the Applicants, namely to use Domenighini to "define" reference sequences

(full-length LT proteins). Accordingly, Applicants were in possession of fragments of particular sizes and particular sequences, as claimed, and, in addition, the new matter rejection is in error and should be withdrawn.

35 U.S.C. § 112, FIRST PARAGRAPH, ENABLEMENT

With respect to the reiterated enablement rejection, the Advisory Action stated (page 4):

> Enablement rejection of claims 7-29 under 35 U.S.C. § 112 first, as containing subject matter [*sic*] is maintained. Applicant submits the prior art references submitted to demonstrate toxicity of fragments with replaced Ala-72 are "entirely irrelevant" as long as applicant point out which residue (Ala-71) is to be mutated. Examiner disagrees. The instant application demonstrates that full length LT-A has reduced toxicity as compared to wild-type (Figs. 4 and 5), but does not demonstrate any octamers of LT-A t hat are detoxified compared to wild-type LT-A. Prior art, on the other side, teaches that LT-A derivatives having Ala72 replaced with Arg72 remain to be toxic. Further, there is on description in the claims or specification sufficiently identifying epitope sequence. Consequently, there is no guidance on what fragments are required to maintain immunogenicity and, at the same time, possess reduced toxicity.

For the reasons of record and those presented below, Applicants traverse the rejection and supporting remarks.

References

The Advisory Action misconstrues Applicants arguments with respect to the references cited to show unpredictability and the teachings of these references themselves.

Applicants did not argue that the references are irrelevant so long as the residue to be mutated was pointed out. Rather, Applicants argued that the references cited as allegedly establishing unpredictability were irrelevant because they present data that direct contrasts to the data of the specification. *See,* footnote 1 in Response After Final. Furthermore, the specification findings (detoxification by mutation Ala72 to Arg72) are supported by many subsequent publications. Simply put, the references cited by the Examiner do not establish unpredictability because, with respect to the Ala-72 to Arg-72 mutation they have been proven wrong and are inapplicable to the case at hand.

Guidance Regarding Epitope Sequences

The Advisory Action also erroneously asserts that the specification must identify "epitope" sequences and that there is no guidance on what fragments are required to maintain immunogenicity and, at the same time, possess reduced toxicity. (Advisory Action, page 4).

In fact, the specification provides ample guidance on the nature of the claimed fragments, both in terms of structure and function. Structurally, they must comprise at least contiguous 8 amino acids of a particular reference sequence (*e.g.* ,SEQ ID NO:1); the 8 amino acids must include the Ala-72 residue; and the Ala-72 residue must be mutated into an arginine. Functionally, the claimed fragments must be both detoxified and immunogenic.

The specification as filed provides ample guidance on how to identify fragments having the claimed structure and function. *See,* Response After Final, filed November 9, 2004.

Inoperative Embodiments

Applicants reiterate that the presence of inoperative embodiments does not necessarily render a claim nonenabled. *See, e.g.,* MPEP § 2164.08(b); and *In re Angstadt,* 537 F.2d 498, 504, 190 USPQ 214, 219, CCPA 1976. The test of enablement is not what is predictable *a priori*, but what the specification teaches the skilled practitioner in regard to the claimed subject matter. Thus, not every species (or even a majority of species) encompassed by the claims, even in an unpredictable area like the chemical sciences, needs to be disclosed. *In re Angstadt,* 537 F.2d 498, 504, 190 USPQ 214, 219, CCPA 1976. The notion that one of ordinary skill in the art must have reasonable assurances of obtaining positive results on every occasion has been emphatically rejected. *Angstadt* at 219. So long as it is clear that some species render the claims operative, the inclusion of possible inoperative species cannot invalidate the claim under paragraph 1 of 35 U.S.C. §112. *See, also, In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, CCPA 1971; *Horton v. Stevens*, 7 USPQ2d 1245, 1247, Fed. Cir. 1988.

In the pending case, Applicants again note that every fragment falling within the scope of the claims can be determined *a priori* and, as such, the entire genus of claimed fragments is enabled

by the specification as filed.[1] Thus, there are no inoperative "structural" embodiments encompassed by the claims and, as such, the specification clearly enables the structures (sequences) of the claims.

Moreover, as set forth in the case law described above, the possibility that there may be some inoperative "functional" embodiments (*e.g.*, some of the polypeptides may not be immunogenic) does not render the specification nonenabling because the specification clearly teaches how to test for immunogenicity and indicates that such testing is utterly routine. Routine experimentation, as would be required to determine if an embodiment falls within the "functional" scope of the claims, is not undue experimentation.[2]

Thus, not only does the claim language itself exclude inoperative embodiments, namely any and all fragments that are not immunogenic and detoxified, the experimentation needed to identify inoperative embodiments is not undue. Accordingly, the presence of potentially inoperative functional embodiments cannot form grounds for rejecting the pending claims as allegedly nonenabled.

Simply put, the claimed fragments will be detoxified by virtue of the mutation at the specified residue, a finding set forth clearly in the specification as filed. Further, the immunogenic nature of any detoxified fragment can be readily tested and it is improper for the Office to require working examples to establish enablement.[3] Any "inoperative" embodiments are excluded from the scope of the claims and can be identified as such using routine experimentation.

Thus, the specification as filed more than amply satisfies the enablement requirement of Section 112, as one of skill in the art could make and use the claimed molecules without undue experimentation following the guidance set forth in the.

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[1] Applicants also direct the Examiner's attention to Example N:DNA of the Patent Office's "Training Materials for Examining Patent Applications with respect to 35 U.S.C. § 112, First Paragraph -- Enablement -- Chemical/Biotechnical Applications," which states that even with a very large genus of sequences (at least 1.26×10^{21}), undue experimentation is not required to determine all members of the genus because "each embodiment can be readily identified using the genetic code, synthesized using conventional methods, and used in the manner taught in the specification." see, page N-4.

[2] *See, also, United States v. Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied,* 490 U.S. 1046 (1989)), holding that routine experimentation, even if extensive (on the order of six or more months and tens of thousands of dollars), is not necessarily undue.

[3] Applicants also note that the Examiner has not addressed references previously submitted (*e.g.*, Habeeb, Stylos), which references provide explicit evidence that analysis of peptide fragments for their immunogenicity was routine at the time of filing.

35 U.S.C. §§ 102/103

Claims 7-29 were also again rejected as allegedly unpatentable over EP 145486. The arguments regarding the fact that this reference does not teach fragments as claimed was **not** addressed and is therefore, reproduced herein.

Applicants reiterate that the Examiner is not entitled to read claim limitations in a vacuum. In particular, it is error to read the limitation regarding the mutation (Ala to Arg) at the position corresponding to Ala-72 without considering the position (residue 72) specified in the claim.

Therefore, when the claim is properly read as a whole, it is clear that not any alanine residue can be replaced with an arginine residue. Indeed, the claims not only require replacement of a residue "corresponding to" an alanine residue with an arginine residue, the claims (and specification) specify the particular position of the alanine that must be replaced, with respect to a reference sequence (SEQ ID NO:1). It is improper to ignore this explicit limitation of position of the alanine and assert that any toxic protein that includes any Ala-Arg substitution reads on the pending claims.

Accordingly, to fall within the scope of the claims, the fragment must include SLRSAHL**R** or **R**GQSILSG (where the bolded R indicates the replaced Ala at position 72. Such fragments are not disclosed in EP145486. In fact, in EP145486, the alanine residue corresponding to Ala-72 of SEQ ID NO:1 remains an alanine (see, residue 89 of the sequence cited in paragraph 6 of the Final Office Action).

Thus, even if the rejection had not been previously withdrawn, it is improper and should be withdrawn.

CONCLUSION

In view of the foregoing, Applicant submits that the claims are now in condition for allowance and requests early notification to that effect. Please direct all further communications regarding this application to:

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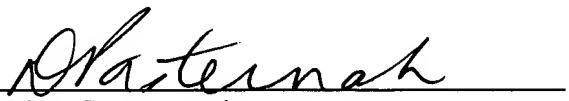
Respectfully submitted,

Date: December 15, 2004

By: 

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